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Subject: Comments to the Draft Guidelines for the Prevention of Intravascular Catheter-Related Infections

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First, on behalf of all the people, both clinicians and patients, who will benefit from these updated Guidelines, I'd like to thank each of the members of the CDC HICPAC Committee for the enormous effort they put into the development of this document. I also thank the committee for the opportunity to comment on this draft and hope my inputs will serve to make the document as comprehensive and up to date as possible.

I've divided my comments into two types. First are general comments that address topics covered throughout the draft; next are comments related to specific text. Should any member of the committee wish to discuss any of my comments below, please feel free to reach me using the contact information above.

General Comments

1. "Chlorhexidine" is mentioned extensively in this draft. Since there are other salts of chlorhexidine besides that which is currently used in the healthcare setting (e.g. chlorhexidine acetate), I would suggest that in each instance "chlorhexidine" is used, it be replaced with "**chlorhexidine gluconate**" – the specific salt actually incorporated into the products currently used for catheter site care. Without proof of efficacy, it would be inappropriate for this or any other guidance document to unintentionally recommend the use of antiseptic products containing other salts of chlorhexidine. Related to this suggestion would be to use the abbreviation "**CHG**" after the first use of this term.

2. While it's always the case that Standards and Guidelines which get published over time vary in their recommendations due to the information available at the time of their publication, I am concerned that in cases where the proposed CDC Guidelines differ from Standards and Guidelines previously published by other organizations such as the Infusion Nurses Society (INS), The Institute for Healthcare Improvement (IHI), The Society for Healthcare Epidemiology of America (SHEA), and the Association for Professionals in Infection Control and Epidemiology (APIC), clinicians will be conflicted as to what to follow.

   As a result, I would urge that to the extent possible, the updated CDC Guidelines be harmonized with all previously published Standards and Guidelines. When, in fact, these CDC Guidelines contain recommendations that differ from current but previously published Standards and Guidelines, I would urge that those differences be identified and the rationale for each difference be explained and supported by information (preferably evidence-based) presumably not available at the time the earlier Standards and Guidelines were published.

3. Lines 67 – 69 state that "each recommendation [contained in the draft guidelines] is categorized on the basis of existing scientific data, theoretical rationale, applicability, and economic impact". However, the economic impact of a practice is highly setting dependent; i.e., practices that might be cost effective in an Intensive Care Unit may not be at all cost effective in the home healthcare environment. As such, I'm concerned that without an explanation of the healthcare setting(s) in which the economic considerations were made (and therefore apply to), practitioners may be directed to engage in practices which are not cost effective in their specific setting of care.

4. As is indicated in Art, GR. Comparison of the safety and efficacy of two topical antiseptic products: chlorhexidine gluconate + isopropyl alcohol (CHG+IPA) and povidone-Iodine + isopropyl alcohol (PVP-I +IPA). JAVA 2007;12(3):156-163 (available at http://www.aplicare.com/Documents/Art-JAVA2007-V12(3)-pp156-163_CHG-IPA_vs_PVP-IPA_for_Web.pdf#toolbar=0 and attached to the email in which these comments are provided), while making generalities about the relative effectiveness of different antiseptic active ingredients is tempting (e.g., chlorhexidine gluconate is more effective than, or preferred over povidone-iodine), it's important to understand that antiseptic active ingredients are not delivered to the skin by themselves; they're delivered in products consisting of specific volumes of distinct formulations consisting of various active and inactive ingredients with specific application instructions. The FDA recognizes this and in those instances where a new drug is approved for use, the approval is limited to the dosage and delivery instructions for which data is presented.

   From this follows the fact that the actual safety and effectiveness of any particular antiseptic product is dependent on a wide variety of factors including:

   a) The concentration of the active ingredient. In most cases, the higher the concentration of active ingredient(s), the greater the efficacy, but generally also the greater the irritation potential and cost.

   b) The presence or absence of additional active ingredients and the possible synergistic or deleterious effects between actives having different modes of action. This is especially important when the additional active(s) is (are) either ethyl alcohol (EtOH) or isopropyl alcohol (IPA) at concentrations considered by the FDA to be effective antiseptic ingredients (EtOH – 60%-95%; IPA – 70%-91%) – see FDA's Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products (available at http://www.aplicare.com/Documents/FDA-Healthcare_Antiseptic_TFM_1994.pdf).

   c) The presence or absence of various inactive ingredients (e.g., buffering and film-forming agents, surfactants, emollients, colorants, fragrances) included in the formulation. Many surfactants and emollients deactivate certain antiseptic agents. For example, chlorhexidine gluconate is deactivated by anionic surfactants and must be formulated only with cationic or ionically neutral ingredients. A chlorhexidine gluconate formulation containing anionic ingredients would essentially be no more effective than plain soap. pH can also have a substantial influence on the efficacy of an antiseptic formulation. The presence or absence of film-forming agents which can cause antiseptic ingredients to remain in contact with the skin for longer periods of time can influence a product's persistence. Thickening agents can lead to less of the formulation running off the treatment area before killing any microorganisms. In other words, not all formulations containing the same active ingredient(s), even at the same concentrations, can necessarily be expected to perform the same.

d) The time the antiseptic formulation is in contact with the skin (i.e., the application time). In most cases, the longer the antiseptic is in contact with the area being treated, the more bacteria are killed. This, of course, typically comes at a cost in terms of procedure time and greater irritation potential.

e) The volume of solution applied relative to the area of skin being treated. One would not expect to be able to prep an entire leg or chest with 1 mL of any antiseptic formulation – regardless of which active ingredients are present.

f) The manner in which the formulation is applied (e.g., firm scrubbing vs. gentle painting; back and forth motion vs. circular motion). More aggressive scrubbing allows for greater penetration of the antiseptic into deeper layers of the skin where some microorganisms exist. However, excessive scrubbing can also lead to the skin being damaged; resulting in the creation of an environment favorable to the regrowth of microorganisms.

g) The shape and abrasiveness of the delivery system (typically rayon or foam-tipped applicator) used to apply the formulation to the skin. The abrasiveness of applicators can affect the extent to which an antiseptic penetrates into deeper layers of the skin with the same level of force applied.

An important insight resulting from the above is that since manufacturers qualify their products using the labeled directions for use, it's critical that clinicians follow these directions. Otherwise, they cannot be assured that the product will perform as expected.

As a result, and consistent with section 41 (G-Access Site Preparation) of the current 2006 INS Standards of Practice, which states "The process for applying the chosen antiseptic agent is dependent upon and should be consistent with the manufacturer's labeled use(s) and directions." and section 51(E-Catheter Site Care), which states "Antiseptic solutions should be used in accordance with manufacturer's labeled use(s) and directions.", I would strongly recommend that the final Guidelines include a statement to the effect that "**No antiseptic product should be used unless it is appropriately sized for the intended procedure and the directions for use that appear on the label can and will be followed.**"

Another important point related to the above is the realization that contrary to what is suggested in many journal article titles (and summary conclusions), studies actually don't compare active ingredients or even formulations; they compare specific products and protocols. In addition, because the above factors become test variables in the evaluation of any particular active ingredient, by varying the above parameters, it's relatively easy to demonstrate superiority of one active ingredient over *any* other. As a result, erroneous conclusions can easily be derived with the best of intentions (see comment #6 below).

5. Related to comment #4b above, I applaud the committee for including the languages used on lines 424 – 425 of the draft guidelines recommending the use of 70% alcohol before peripheral catheter insertions. In spite of being considered by the CDC's current Guidance for the Prevention of Surgical Site Infections (http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf) to be "the most effective and rapid-acting skin antiseptic"(p. 257), the alcohols at concentrations considered by the FDA to be effective antiseptic ingredients [EtOH – 60%-95%; IPA – 70%-91% – see FDA's Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products (available at

http://www.aplicare.com/Documents/FDA-Healthcare_Antiseptic_TFM_1994.pdf)] are, in my opinion, the most underrated antiseptic active ingredients available for a number of reasons:

a) Contrary to conventional wisdom, while the alcohols evaporate almost immediately upon application, they are *functionally* persistent (defined as slowing the rate of regrowth of bacteria remaining on a previously treated site) if (as is the case with treated catheter insertion sites) the site is immediately covered by a semi-permeable transparent dressing after the product is applied and allowed to dry. This occurs by virtue of the alcohols being extremely fast acting, broad spectrum (kill a wide variety of microorganism species), and substantive (kill a large number of microorganisms). Their application results in the vast majority of surviving bacteria being rendered incapable of reproduction for an extended period of time; the application of a semi-permeable transparent dressing prevents contamination from exogenous sources.

   This assertion is supported by data developed during the definitive human clinical studies required by and submitted to the FDA as part of the New Drug Application (NDA# 20-832) for ChloraPrep (combination formulation containing 2% chlorhexidine gluconate and 70% isopropyl alcohol) which showed no difference whatsoever in either the immediate (one minute post-product application) or persistent (6 and 24 hours post-product application) efficacy between the combination formulation containing 2% chlorhexidine gluconate and 70% isopropyl alcohol and 70% isopropyl alcohol alone – see Table 3 on page13 of the attached Microbiology Review of the ChloraPrep NDA originally available at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP%20ONE-STEP%20ANTISEPTIC_microbredr.pdf, and now available at http://www.aplicare.com/Documents/20-832_CHLORAPREP_ONE-STEP_ANTISEPTIC_microbr.pdf.

b) The alcohols (EtOH – 60%-95%; IPA – 70%-91%) offer the additional benefit of reducing procedure time by causing formulations that contain them to dry more rapidly.

Recognizing the benefits of including alcohol in combination with both CHG and PVP-I formulations, the 2006 Infusion Nursing Society's *Standards of Practice* state "**Formulations containing a combination of alcohol (ethyl or isopropyl) and either chlorhexidine gluconate or povidone-iodine are preferred**" for access site preparation (Standard 41) and catheter site care (Standard 51). I would urge the CDC guidelines adopt similar language.

6. Related to comments #4 and #5 above, I would respectfully submit that many of the studies cited in the draft guidelines to support the recommended practices in Lines 421 – 456 and Lines 1431 – 1446 ("Skin Preparation") actually do not support what is recommended.

   a) Reference [140 – Maki] showed that if three products were used in the same manner, the product containing aqueous 2% chlorhexidine gluconate performed better than those containing either 10% povidone-iodine or 70% isopropyl alcohol. However, without knowing what other ingredients were in these products, it's impossible to know whether it was actually the active ingredients responsible for the outcomes or one or more of the other six factors listed above in comment #4.

First, specific to comment #4d, the application instructions employed in the Maki study (each antiseptic applied for 30 seconds) were not what was typically used at the time of the study, nor what is typically used today. According to Melissa Leone, National Director of Nursing Operations at Coram Specialty Infusion Services, the use of swabsticks saturated with isopropyl alcohol followed by swabsticks saturated with povidone-iodine was the most common practice before clinicians began moving toward the use of 2% chlorhexidine gluconate and 70% isopropyl alcohol. Typical directions for use for maintaining catheter insertion sites using kits containing swabsticks saturated with isopropyl alcohol and swabsticks saturated with povidone-iodine are:

i. Open packet of alcohol triple swabsticks and cleanse site beginning at the insertion site.
ii. Applying friction, move outward in a circular pattern covering an area of 2" – 4" in diameter for 30 seconds.
iii. Repeat with second swabstick.
iv. Cleanse catheter with third alcohol swab and allow site to dry.
v. Open packet of Povidone-Iodine triple swabsticks and re-cleanse site beginning at the insertion site.
vi. Applying friction, move outward in a circular pattern covering an area of 2" – 4" in diameter for 30 seconds.
vii. Repeat with second and third swabsticks. [Total application time = 90 seconds]
viii. Allow site to air dry.

Second, the use of alcohol alone or povidone-iodine alone was not what was typically used at the time of the study, nor what is typically used today. A survey of the leading central line dressing change kit manufacturers' kit offering (as described on their web sites; (http://www.medical-action.com/catalog/productline.asp?id=325; http://www.cardinal.com/us/en/brands/presource/files/Dressing%20Change%20Kits%202PRE0724.pdf; http://www.medikmark.com/foundations/store/scresults.asp?category=87; http://www.busseinc.com/busse_num_index.htm; http://lslhealthcare.com/images/myimages/1-hpdf.pdf; http://www.aplicare.com/Documents/Aplicare_Advantage_Sell_Sheet_ML0005Dv2.pdf) shows no standard kits which contain swabsticks saturated with povidone-iodine without also containing swabsticks saturated with isopropyl alcohol and no standard kits which contain swabsticks saturated with isopropyl alcohol without also containing swabsticks saturated with povidone-iodine.

Thus, the Maki study only showed an aqueous formulation of 2% chlorhexidine to be superior to that which was at the time, and currently is not done in practice.

Again, this example provides good reason why it's critical that the proposed Guidelines state something consistent with section 41 (G-Access Site Preparation) of the 2006 INS Standards of Practice which state "**The process for applying the chosen antiseptic agent is dependent upon and should be consistent with the manufacturer's labeled use(s) and directions.**" and section 51(E-Catheter Site Care) which states "**Antiseptic solutions should be used in accordance with manufacturer's labeled use(s) and directions.**".

b) Reference [141 – Mimoz] did not compare the effectiveness of chlorhexidine gluconate to povidone-iodine. Instead, they compared a combination formulation of chlorhexidine gluconate, benzalkonium chloride, and benzyl alcohol to 10% povidone-iodine when applied

for only 30 seconds prior to the insertion of the catheter – again, not evaluating a formulation containing solely chlorhexidine gluconate and not employing the typical directions for use for the product containing povidone-iodine. Further, the authors don't state what skin preparation procedure was used during catheter site maintenance.

c) Reference [142 – Humar] does not indicate whether the alcohol content of the combination formulation was at a level considered by the FDA to be effective (ethyl alcohol between 60% and 95% or isopropyl alcohol between 70% and 91% - see FDA's Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products (available at http://www.aplicare.com/Documents/FDA-Healthcare_Antiseptic_TFM_1994.pdf). They also only treated the catheter insertion sites for 20 – 30 seconds with each product; again, not what is typically done with povidone-iodine based products.

d) A careful review of the studies included in the meta-analysis reported in Reference [143 – Chaiyakunapruk] shows that the "deck was stacked" against 10% povidone-iodine by comparing it not to formulations containing chlorhexidine gluconate alone, but in most cases, to those containing a combination of chlorhexidine gluconate and alcohol and/or one more other active ingredients. Those studies and their shortcomings (as it relates to drawing the conclusion that formulations containing chlorhexidine gluconate are superior in reducing catheter related bloodstream infections when compared to povidone-iodine are:
    i. Sheehan G, Leicht K, O'Brien M, Taylor G, Rennie R. Chlorhexidine versus povidone-iodine as cutaneous antisepsis for prevention of vascular-catheter infection [Abstract]. In: Program and Abstracts—Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Soc for Microbiology; 1993:414(a1616). Reference could not be located to determine whether either alcohol was included in the chlorhexidine formulation or how long the povidone-iodine was applied. Without this information, accurate conclusions cannot be drawn.
    ii. Meffre C, Girard R, Hajjar J, Fabry J. Is peripheral venous catheter colonization related to the antiseptic used for disinfection of the insertion site? Povidone-iodine vs. alcoholic chlorhexidine: a multicenter randomised prospective study [Abstract]. Catheter Study Group. Hygienes. 1995;9:45. Reference could not be located, but the title indicates that the chlorhexidine formulation also contained alcohol.
    iii. Mimoz et al. [draft guidance reference #141] – see comments immediately above; the povidone-iodine was only applied for 30 seconds vs. common practice of at least 90 seconds (see comment #6avii above); the chlorhexidine formulation also contained benzalkonium chloride, and benzyl alcohol. The chlorhexidine gluconate-containing product is not approved by the FDA for any use.
    iv. Legras A, Cattier B, Dequin PF, Boulain T, Perrotin D. Etude prospective randomisee pour la prevention des infections liees aux catheters: chlorhexidine alcoolique contre polyvidone iodee. Reanimation et Urgences. 1997;6:5-11. Reference could not be located, but the title indicates that the chlorhexidine formulation also contained alcohol.
    v. LeBlanc A, Cobett S. IV site infection: a prospective, randomized clinical trial comparing the efficacy of three methods of skin antisepsis. Canadian Intravenous Nurses Association Journal. 1999;15:48-50. Reference could not be located, but a study published in Can J Infect Con (Spring:9-14) the next year by the same authors was entitled "A 0.5% chlorhexidine gluconate in 70% isopropyl alcohol swab was more effective than 2 other methods for intravenous skin antisepsis".

vi. Knasinski V, Maki DG. A prospective, randomized, controlled trial of 1% chlorhexidine 75% alcohol vs. 10% povidone iodine for cutaneous disinfection and follow-up site care with central venous and arterial catheters [Presented paper]. San Diego: National Association of Vascular Access Network Conference; 2000. Reference could not be located, but the title indicates that the chlorhexidine formulation also contained alcohol. The chlorhexidine gluconate-containing product is not approved by the FDA for any use.

e) Reference [144 – Chaiyakunapruk] used the same studies to derive their conclusions as were used in reference [143 – Chaiyakunapruk], and thus has the same shortcomings.

Comparing active ingredients where one of the ingredients is always paired with an additional active is like comparing preferences toward strawberry vs. vanilla ice cream with hot fudge and concluding that people prefer vanilla ice cream. Such a study does not demonstrate that vanilla ice cream by itself is preferred over strawberry – only that vanilla with hot fudge is preferred over strawberry.

If used per the manufacturer's directions for use, formulations containing chlorhexidine gluconate alone are more effective than formulations containing povidone-iodine alone. But if either the formulation containing chlorhexidine gluconate or the formulation containing povidone-iodine also contains alcohol (considered by the CDC's current Guidance for the Prevention of Surgical Site Infections to be "the most effective and rapid-acting skin antiseptic"), the formulation containing the alcohol will be more efficacious because of the alcohol content – see Art, GR. Comparison of the safety and efficacy of two topical antiseptic products: chlorhexidine gluconate + isopropyl alcohol (CHG+IPA) and povidone-Iodine + isopropyl alcohol (PVP-I +IPA). JAVA 2007;12(3):156-163 (available at http://www.aplicare.com/Documents/Art-JAVA2007-V12(3)-pp156-163_CHG-IPA_vs_PVP-IPA_for_Web.pdf#toolbar=0 and attached to the email in which these comments are provided).

7. Not all topical antiseptic products are appropriate for, or have been approved or cleared for use by the FDA for all possible uses. For example, one would not use Hibiclens® (4% aqueous chlorhexidine gluconate in a detergent base; typically used for healthcare personnel handwashing and surgical hand scrubbing) for catheter site maintenance; nor would one use ChloraPrep® (combination 2% chlorhexidine gluconate and 70% isopropyl alcohol) as a healthcare personnel handwash. As a result, I would strongly recommend that the final Guidelines include a statement to the effect that "**No antiseptic product should be used unless approved or cleared by the FDA and labeled for the intended use**."

8. While many studies have reported the efficacy of formulations containing chlorhexidine gluconate alone or in combination with alcohol, I am concerned that chlorhexidine gluconate's pervasive use will lead to the emergence of resistant strains as well as individuals in the population becoming allergic to it with repeated exposure.

Over the years, there have been various reports of allergic reactions to chlorhexidine gluconate. The FDA issued a Public Health Notice, FDA Public Health Notice: Potential Hypersensitivity Reactions To Chlorhexidine-Impregnated Medical Devices (see http://www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/ucm062306.htm and referenced articles) identifying anaphylactoid and other types of reactions associated with

chlorhexidine. The Public Health Notice references incidences that occurred in Japan, Switzerland, the United Kingdom, Australia, Malaysia and the US. Okana et al report 6 cases in which chlorhexidine gluconate use resulted in anaphylactic symptoms when used to prep various anatomical sites from vaginal to facial skin prep. Thune reports of a 15 year old girl who developed an eczematous reaction after long term use of anti-acne solution containing chlorhexidine gluconate. Yong et al note that "Our experience suggests that this serious adverse drug reaction is under-reported…" In the studies or abstracts referenced in the FDA Public Notice that I was able to review, chlorhexidine gluconate was confirmed to be the causative agent for the allergic reaction.

As such, I would warn against the Guideline's emphasis of chlorhexidine gluconate's use to the exclusion of the Category 1A topical antiseptics (strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies) listed in the 2002 Guidelines (i.e., 2% CHG, tincture of iodine, iodophors, 70% alcohol) – especially those containing a combination of povidone-iodine and isopropyl alcohol which was shown in Art, GR. Comparison of the safety and efficacy of two topical antiseptic products: chlorhexidine gluconate + isopropyl alcohol (CHG+IPA) and povidone-Iodine + isopropyl alcohol (PVP-I +IPA). JAVA 2007;12(3):156-163 (available at http://www.aplicare.com/Documents/Art-JAVA2007-V12(3)-pp156-163_CHG-IPA_vs_PVP-IPA_for_Web.pdf#toolbar=0 and attached to the email in which these comments are provided) to be equally effective and less irritating than a formulation containing a combination of 2% chlorhexidine gluconate and alcohol.

9. The committee should be aware that the FDA draws a marked distinction between topical antiseptics used for the preparation of central venous catheter insertion sites based on their use and corresponding potential to cause irritation:

    a) "One time use" products for preparation of the skin prior to the insertion of a catheter – considered by the FDA to be a surgical procedure.

    b) Multiple use products for preparation of the skin between dressing changes as part of the maintenance of catheter insertion sites.

This assertion can be substantiated by contacting Dr. Charles Ganley, MD, Director, Center for Drug Evaluation and Research, Office of New Drugs, Office of Nonprescription Products (Tel: 301-796-2060; Fax: 301-796-9899; email: charles.ganley@fda.hhs.gov)

While there are many products containing chlorhexidine gluconate and other antiseptic active ingredients available on the market for preparing the skin prior to surgery (labeled "For preparation of the skin prior to surgery" and/or "Patient Preoperative Skin Preparation"), **the FDA has not approved any chlorhexidine-based preparations for the maintenance of catheter sites**. Specifically, with respect to the only 2% chlorhexidine-based preparation marketed in the United States for catheter site maintenance (ChloraPrep®, CareFusion, Corp.) in its Medical Review of the ChloraPrep New Drug Application (originally available at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP%20ONE-STEP%20ANTISEPTIC_medr.pdf, and now available at http://www.aplicare.com/Documents/20-832_CHLORAPREP_ONE-STEP_ANTISEPTIC_medr.pdf), the FDA explicitly states:

> *In the Clinical Review of this NDA dated December 23, 1997, the Safety Summary noted that ChloraPrep demonstrated a relatively high potential to cause irritation and sensitization reactions in predictive skin testing. It scored*

> *much higher in irritancy testing than Hibiclens [an aqueous 4% chlorhexidine gluconate preparation]. [text redacted by FDA] Concern was also voiced that repeated use could exacerbate the irritation/sensitization possibilities.*
>
> *These concerns have been satisfied by the decision to indicate the product for use as a patient preoperative skin preparation. This is a one time use [text redacted by FDA] Thus, while the product is irritating, its intended indication [as a one time use product] does not prohibit its use. The margin for safety available to the patient under these [one time use] conditions is acceptable.*

The following question to Dr. Ganley would confirm the above assertion: "Is ChloraPrep® approved for use by the FDA as a central venous catheter site maintenance preparation?"

10. If, after reviewing comment #9, the committee decides to recommend the off-label (i.e., not approved by the FDA) use of products containing 2% chlorhexidine gluconate and 70% isopropyl alcohol for catheter site maintenance, I would strongly urge that when reference is made to the use of "a 2% chlorhexidine preparation", the language be changed to "**a preparation containing at least 2% chlorhexidine gluconate and at least 70% isopropyl alcohol**". My reasons for this are as follows:

    a) With the exception of the study published by Maki et al. (current draft guidance reference [140] which evaluated an aqueous based 2% chlorhexidine formulation [according to Dr. Maki, never commercialized], all the studies referenced in the draft Guidelines to support the use of "a 2% chlorhexidine preparation" are actually based on the evaluation of formulations containing 2% chlorhexidine gluconate and 70% isopropyl and/or some other active(s) – see earlier comment.

    b) As indicated in comment #4b, the distinction between an aqueous 2% chlorhexidine formulation and one containing at least 70% isopropyl alcohol is significant in that 70% isopropyl alcohol is, in fact, an extremely effective antiseptic and therefore makes a significant contribution to the efficacy of the formulations in which it is present. Indeed, the CDC's current Guideline for the Prevention of Surgical Site Infections (http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf) considers alcohol to be "the most effective and rapid-acting skin antiseptic". When this Guideline was published in 1999, chlorhexidine gluconate in the form of Hibiclens® had already been available in the United States for 22 years. The CDC's current Guideline for the Prevention of Surgical Site Infection identified alcohol to be "the most effective and rapid-acting skin antiseptic" over a chlorhexidine gluconate containing formulation not containing alcohol.

    c) There are no antiseptic products available on the market in the United States for catheter site maintenance that consist of an aqueous formulation of 2% chlorhexidine gluconate with no active levels of isopropyl alcohol. All available aqueous formulations containing 2% chlorhexidine gluconate also contain detergents and are intended for patient preoperative prepping, surgical hand scrubbing, and healthcare personnel handwashing where the product is either rinsed or wiped off the skin after application.

11. "Povidone iodine" should be spelled with a hyphen; i.e., "Povidone-iodine"

Comments Related to Specific Sections of the Draft Guidelines

Re: Lines 36 – 54: While the list of participating organizations involved in the development of these draft guidelines is impressive, given the trend of patients migrating from the acute to home care environments, I would submit that one additional and important organization which should be consulted is the National Home Infusion Association (www.nhia.org). Practitioners need to be advised that what might be appropriate in the acute care environment may not be appropriate when patients are discharged to the home. The individual best qualified within NHIA to contact is Nancy Kramer, RN, BSN, CRNI®, Vice President of Clinical Affairs ((703) 549-3740; nancy.kramer@nhia.org).

Re: Lines 83 – 85: The 15 million CVC day estimate is based on a study published in 2000, now ~10 years old. Given the growth of the US population and changing demographics, this number must now be higher. However, without more time before the comment period deadline, I was unable to locate more current information.

Re: Lines 371 – 372 and 1406 - 1407: I presume the use of the term "waterless" with respect to ABHRs refers to the fact that water is not needed during these products' application or use. However, the term also implies that the products themselves do not contain water – which, of course, they do. As such, the following language might be more applicable: "**Perform hand hygiene procedures, either by washing hands with conventional antiseptic containing soap and water or alcohol-based hand rubs (ABHR) which do not require the use of water during or after application.**"

Consistent with comment #2 above, I would urge the language used in the final Guidelines either be modified to incorporate that which is in the Infusion Nurses Society's 2006 Standards of Practice with deviations explained; specifically (paraphrasing)…

1. **Hand hygiene should be a routine practice and performed before and immediately after all clinical procedures, and before donning and after removal of gloves.**
2. **Products used should provide high efficiency with low potential for skin irritation and be used according to the manufacturer's labeled use(s) and directions.; towelettes and non–alcohol-based hand rubs should not be used.**
3. **Alcohol-based hand rubs or hand washing with soap and water are appropriate for hand decontamination when hands are not visibly soiled, before direct contact with the patient's intact skin, before performing aseptic infusion procedures, after contact with objects or equipment in the patient's immediate vicinity, and after removing gloves.**
4. **Bar soap should not be used as it is a potential source of bacteria; however, liquid soap and water are adequate.**
5. **Dispensers of liquid soap or antiseptic solutions are recommended.**
6. **Single-use soap scrub packets or waterless antiseptic products should be used when running water is compromised or unavailable.**
7. **Clinicians should not wear artificial nails or nail products when performing infusion therapy procedures.**
8. **In cases where clinician's hands are visibly contaminated with blood or body fluids, hand hygiene with either non-antiseptic or antiseptic (preferably antiseptic-containing) liquid soap and water should be performed.**

Re: Lines 380 – 382: I have significant concerns about the potential for "clean" gloves to be a vector for the transfer of microorganisms. To avoid the possibility of microorganisms being deposited onto gloves during the manufacturing process, at a minimum, the gloves should be sterile at the time of receipt by the clinician. Regardless, as worded, the current language could be interpreted to mean that

clean gloves are preferable to sterile gloves for the insertion of peripheral catheters. At a minimum, the language should read "**Clean gloves, rather than sterile gloves can be worn for the insertion of peripheral intravascular catheters…**" That said, is the economic benefit of using "clean" vs. sterile gloves worth the risk? What study/studies support this?

Re: Lines 383 and 387: Both items are labeled "4"

Re: Lines 387 – 388: I have significant concerns about the potential for "clean" gloves to be a vector for the transfer of microorganisms to the patient's skin. To avoid the possibility of microorganisms being deposited onto gloves during the manufacturing process, at a minimum, the gloves should be sterile at the time of receipt. Is the benefit worth the risk? What study/studies support this?

Re: Lines 392 – 393: I presume the use of the term "waterless" refers to the fact that water is not needed during their application or use. However, the term also implies that the products themselves do not contain water – which, of course, they do. Perhaps the following language would be more appropriate: "**Proper hand hygiene can be achieved through the use of either an alcohol-based product [135] requiring no water during or after application or an antibacterial soap and water with adequate rinsing [127].**"

Re: Lines 394 – 398: I have significant concerns about the potential for "a new pair of disposable nonsterile" gloves being a vector for the transfer of microorganisms. Can we (or do we want to) rely on clinicians always effectively employing a "no-touch" technique? Is the benefit worth the risk? What study/studies support this?

Re: Lines 424 – 425: As mentioned previously, regardless of the antiseptic to be used subsequently, this is an outstanding recommendation as alcohol is already considered by the CDC's current Guideline for the Prevention of Surgical Site Infections (http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf) to be "the most effective and rapid-acting skin antiseptic". Additionally, the use of alcohol-impregnated swabs prior to the use of povidone-iodine swabs for catheter site maintenance is consistent with what many clinicians use today and what most did before converting over to the use of a formulation containing 2% chlorhexidine gluconate and 70% isopropyl alcohol.

Re: Lines 424 – 425: I would respectfully submit that the committee has overlooked another combination antiseptic product equally as effective, less irritating, and generally less expensive than formulations containing 2% chlorhexidine gluconate and 70% isopropyl alcohol; specifically formulations containing a combination of povidone-iodine and isopropyl alcohol. For a review of the literature related to formulations containing a combination of povidone-iodine and isopropyl alcohol, see Art, GR. Combination povidone-iodine and alcohol formulations more effective, more convenient versus formulations containing either iodine or alcohol alone. J Infus Nurs. 2005;28(5):314-319 attached to the email in which these comments are provided.

The only study that I am aware of which has compared the safety and efficacy of a PVP-I + alcohol formulation to a formulation containing CHG + alcohol is Art, GR. Comparison of the safety and efficacy of two topical antiseptic products: chlorhexidine gluconate + isopropyl alcohol (CHG+IPA) and povidone-Iodine + isopropyl alcohol (PVP-I +IPA). JAVA 2007;12(3):156-163 (available at http://www.aplicare.com/Documents/Art-JAVA2007-V12(3)-pp156-163_CHG-IPA_vs_PVP-IPA_for_Web.pdf#toolbar=0 and attached to the email in which these comments are provided.

Studies demonstrating the superiority of PVP-I + alcohol formulations over formulations containing PVP-I alone are many:

1. Arata, T, Murakami, T, Hirai, Y. Evaluation of povidone-iodine alcoholic solution for operative site disinfection. Postgrad Med J. 1993;69(Suppl 3):S93-S96.
2. Birnbach DJ, Meadows W, Stein DJ, Murray O, Thys DM, Sordillo EM. Comparison of povidone-iodine and DuraPrep, an iodophor-in-isopropyl alcohol solution, for skin disinfection prior to epidural catheter insertion in parturients. Anesthesiology. 2003;98(1):164-169.
3. Calfee DP, Farr BM. Comparison of four antiseptic preparations for skin in the prevention of contamination of percutaneously drawn blood cultures: a randomized trial. J Clin Microbiol. 2002; 40(5):1660-1665.
4. Gilliam DL, Nelson CL. Comparison of a one-step iodophor skin preparation versus traditional preparation in total joint surgery. Clin Orthop Rel Res. 1990;205:258-260.
5. Jeng DK. A new water-resistant, film-forming, 30-second, one-step application iodophor preoperative skin preparation. Am J Infect Control. 2001;29(6):370-376.
6. Jeng OK, Severin JE. Povidone iodine gel alcohol: a 30-second, one-time application preoperative skin preparation. Am J Infect Control. 1998;26(5):488-494.
7. Parietnti JJ, du Cheyron D, Ramakers M, et al. Alcoholic povidone-iodine to prevent central venous catheter colonization: a randomized unit-crossover study. Crit Care Med. 2004;32(3):708-713.
8. Parienti JJ, Ducheyron D, Ramakers M, et al. Prospective randomized trial of 10% povidone-iodine (PVI) versus 5% alcohol plus 5% povidone-iodine (APVI) for prevention of central venous catheter (CVC) colonization. Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 2002; 42:318.

Re: Lines 430 and 431: Consistent with the above comments, I would urge the language be changed to "**safety and efficacy of chlorhexidine gluconate based formulations in infants…**"

Re: Lines 432 – 433: The statement as written suggests that povidone-iodine is not effective unless it is in contact with the skin for at least 2 minutes and has dried. Since no reference is given, it is difficult to know the basis of this statement. However, while it is true that ***all*** antiseptic products should be allowed to dry (manufacturer's directions should be followed with respect to this issue), this statement regarding povidone-iodine is incorrect.

In its Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products (available at http://www.aplicare.com/Documents/FDA-Healthcare_Antiseptic_TFM_1994.pdf), the FDA requires that manufactures of all antiseptic products including those containing povidone-iodine demonstrate "in-vitro" efficacy of all their antiseptic formulations. These are studies where the antiseptic being tested is challenged in a test tube with known concentrations of various strains of bacteria and assessed, among other things for their rate of kill in an aqueous environment; i.e. the formulations are not allowed to dry. For an overview of how these studies are designed, see pages 4 – 7 of the document at http://www.aplicare.com/Documents/ExCel-AP_Technical_Bulletin_060502.pdf.

The study by Zamora JL, Price MF, Chuang P, Gentry LO. Inhibition of povidone iodine's bactericidal activity by common organic substances: an experimental study. Surgery. 1985;98:25-9 (attached to the email in which these comments are provided) looked at the effects of diluting a 10% povidone-iodine formulation with various organic materials "in-vitro"; specifically fat, pus, and blood and showed that

10% povidone-iodine solution was able to kill bacteria even when diluted 100X in the presence of fat without drying.

Finally, "free iodine" is the chemical entity in povidone-iodine that kills bacteria and is present in solution – see Gottardi W. Iodine and iodine compounds. In: Block SS, ed. Disinfection, Sterilization, and Preservation. 4th ed. Philadelphia: Lea & Febiger; 1991:151-66 attached to the email in which these comments are provided.

Re: Lines 433 – 436: Consistent with some of my earlier comments, the validity of the statement depends on the specific antiseptic product and to some extent, whether it contains alcohol or not. While it is true that ***all*** antiseptic products ***begin*** to work "on contact", none (including formulations containing either chlorhexidine gluconate or chlorhexidine gluconate plus isopropyl alcohol) is entirely effective immediately. If this were the case, the products' directions for use (determined by controlled efficacy studies defined by the FDA) would be "apply solution, allow to dry". However, they are not:

The directions for use for ChloraPrep® (combination 2% chlorhexidine gluconate and 70% isopropyl alcohol approved for preparation of the skin prior to surgery – what the FDA considers the insertion of a central venous catheter to be) are (see http://www.chloraprep.com/pdf/Directions_of_Use/3_mL/3mL_Clear_label.pdf):

- **dry surgical sites** (such as abdomen or arm): Use repeated back-and-forth strokes of the applicator for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately **30 seconds**. Do not blot or wipe away.

- **moist surgical sites** (such as the inguinal fold): Use repeated back-and-forth strokes of the applicator for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately **one (1) minute**. Do not blot or wipe away.

Note that the application time is dependent on the site of application. Also note that moist surgical sites require a **2 minute application time**.

The directions for use for Hibiclens® (an aqueous 4% chlorhexidine gluconate preparation also approved for preparation of the skin prior to surgery – see http://www.hibigeebies.com/about_indications.asp) are:

> Apply HIBICLENS liberally to surgical site and swab for at least two minutes. Dry with a sterile towel. Repeat procedure for an additional **two minutes** and dry with a sterile towel.

The directions for use for several scrub formulations containing 2% chlorhexidine gluconate are:

- Apply product liberally to surgical site and swab for at least **2 minutes**
- Dry with a sterile towel
- **Repeat procedure for an additional 2 minutes** and dry with a sterile towel

Since no antiseptic product can be considered effective unless its directions for use are followed, it is critical that guidelines such as those proposed by the committee state something consistent with section 41 (G-Access Site Preparation) of the 2006 INS Standards of Practice which state "**The process for applying the chosen antiseptic agent is dependent upon and should be consistent with the manufacturer's labeled use(s) and directions.**" and section 51(E-Catheter Site Care) which

states "**Antiseptic solutions should be used in accordance with manufacturer's labeled use(s) and directions.**".

The suggestion to allow antiseptic formulations (especially those containing a combination of chlorhexidine gluconate and isopropyl alcohol) to dry is extremely important for three reasons:

1. The longer any antiseptic is allowed to be present on the skin, the more bacteria it will kill
2. Catheter insertion sites are typically covered with a semi-permeable transparent dressing which adheres to the skin via an adhesive material. This adhesive cannot attach to the skin if it is wet.
3. Formulations containing a combination of chlorhexidine gluconate and 70% isopropyl alcohol have repeatedly been shown to be irritating with repeated use if not allowed to dry completely. Reference is made to the FDA's position in its Medical Review of the ChloraPrep (combination 2% chlorhexidine gluconate and 70% isopropyl alcohol) New Drug Application (originally available at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP%20ONE-STEP%20ANTISEPTIC_medr.pdf, and now available at http://www.aplicare.com/Documents/20-832_CHLORAPREP_ONE-STEP_ANTISEPTIC_medr.pdf), the FDA reviewer explicitly states:

> In the Clinical Review of this NDA dated December 23, 1997, the Safety Summary noted that ChloraPrep demonstrated a relatively high potential to cause irritation and sensitization reactions in predictive skin testing. It scored much higher in irritancy testing than Hibiclens [an aqueous 4% chlorhexidine gluconate preparation]. [text redacted by FDA] Concern was also voiced that repeated use could exacerbate the irritation/sensitization possibilities.

Re: Lines 452 - 456: This statement in the current draft Guidelines supports the point that alcohol makes a significant contribution to the effectiveness of formulations that contain it. Consistent with this observation, it is recommended that all statements related to the use of formulations containing chlorhexidine gluconate be changed to be consistent with the Infusion Nurses Society's 2006 Standards of Practice which state "**Antiseptic solutions that should be used include alcohol, chlorhexidine gluconate, povidone-iodine, and tincture of iodine, as single agents or in combination, used individually or in series. Formulations containing a combination of alcohol (ethyl or isopropyl) and either chlorhexidine gluconate or povidone-iodine are preferred.**"

The information / data used to support the inclusion of formulations containing a combination of alcohol and povidone-iodine as "preferred" was, in part, published in Art GR. Combination povidone-iodine and alcohol formulations more effective, more convenient versus formulations containing either iodine or alcohol alone. J Infus Nurs 2005;28(5):314-319 (attached to the email in which these comments are provided) and later in Art, GR. Comparison of the safety and efficacy of two topical antiseptic products: chlorhexidine gluconate + isopropyl alcohol (CHG+IPA) and povidone-Iodine + isopropyl alcohol (PVP-I +IPA). JAVA 2007;12(3):156-163 (available at http://www.aplicare.com/Documents/Art-JAVA2007-V12(3)-pp156-163_CHG-IPA_vs_PVP-IPA_for_Web.pdf#toolbar=0 and attached to the email in which these comments are provided).

Re: Lines 483 – 486 and 1473 – 1476: I am concerned about the use of the term "sponge". While there are two chlorhexidine-impregnated "dressings" currently on the market, one could argue that only one is a "sponge". Regardless of which of the two might be shown to be more effective, I can envision other comparable products coming to market before the Guidelines are again updated. The term "**dressing**" would probably cover all products that could be introduced; the term "sponge" may not.

Re: Lines 539 and 1479: While I have been a strong proponent of this practice, the committee should be aware that a review of the literature reveals, at best, mixed results in this practice in reducing surgical site infections. See http://www.cfah.org/hbns/archives/viewSupportDoc.cfm?supportingDocID=170, and http://www3.interscience.wiley.com/cgi-bin/abstract/113422541/ABSTRACT

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